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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,343	01/30/2006	Andrzej Lipkowski	7444/73871/GJG	4648

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
06/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,343	LIPKOWSKI ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-9 and 11-16* is/are pending in the application.

4a) Of the above claim(s) *11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 2, 3 and 5-9 in the reply filed on 4/9/2007 is acknowledged. The traversal is on the ground(s) that a product should not be separated from a process of use. This is not found persuasive in this case because the claims lack a special technical feature. Compounds recited in claim 2 including the elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$ are obvious in view of the prior art (see rejection below). Therefore the claims lack unity of invention *a posteriori*. The requirement is still deemed proper and is therefore made FINAL. Claims 2, 3, 5-9 and 11-16 are pending; claims 11-16 are withdrawn.

Specification

2. Applicant is reminded of the proper content of an Abstract of the Disclosure.

3. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

4. Complete revision of the content of the abstract is required on a separate sheet because the current abstract fails to disclose the claimed compounds and compositions.

5. The disclosure is objected to because although the figures are described, the specification does not include as a separate section with heading, a brief description of the drawings. See MPEP § 608.01(f). A reference to and brief description of the drawing(s) is required by 37 CFR 1.74. Appropriate correction is required.

Claim Objections

6. Claims 2, 3 and 5-9 are objected to because of the following informalities: the compound (Tyr-D-Asn-Gly-Phe-NH)$_2$ appears twice in the Markush group in claim 2 . Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2, 3 and 5-9 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the hydrazide linkage between the peptide monomers in the compounds of claim 2. Figures 1 and 2 clearly show the structure of the claimed compounds but this structure is not readily apparent from the claimed formulas. Without the figure, the skilled artisan would not know that the two tetrapeptides are joined C-terminus to C-terminus via a hydrazide linkage. The specification demonstrates that this linkage is essential to the function of the claimed compounds. Amendment of claim 2 to include figure 1 or 2 would overcome this rejection.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 2, 3 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai *et al.* (*Biochem. Biophys. Res. Comm.*, **1979**, *91*, 1239-49) in view of Abbruscato *et al.* (*J. Neurochem.*, **1997**, *69*, 1236-45) and Kanai *et al.* (*J. Biol. Chem.*, **1998**, *273*, 23629-32). Ronai *et al.* teach the tetrapeptide-amide analog of enkephalin H-Tyr-D-Met-Gly-Phe-NH_2 and its opioid activity in guinea pig ileum (abstract). Ronai *et al.* do not teach the elected species (Tyr-D-Met-Gly-Phe-NH-)$_2$. Abbruscato *et al.* teach the compound biphalin, (Tyr-D-Ala-Gly-Phe-NH-)$_2$, an opioid peptide containing two pharmocophores linked by a hydrazine bridge. When administered intracerebroventricularly, biphalin has been shown to be more potent that morphine and capable of crossing the blood-brain barrier (abstract). Abbruscato *et al.* attribute this potency in part to the affinity of the large neutral amino acid carrier for biphalin (page 1244, first column). Kanai *et al.* teach that the large neutral amino acid carrier has affinity for methionine (page 23629, second column). It would have been obvious to one of ordinary skill in the art to substitute methionine for the alanine in biphalin taught by Abbruscato *et al.* in order to mimic the tetrapeptide taught by Ronai *et al.*, satisfying all of the limitations of claim 2. With respect to claim 3, Abbruscato *et al.* teach biphalin in combination with a pharmacologically acceptable carrier, in the form of an aqueous saline solution, and formulated for direct application to the site of analgesic activity including the CNS (see page 1237). The skilled artisan would have been motivated to make this substitution given that the large neutral amino acid carrier has a greater

affinity for methionine than alanine and that the affinity of this receptor for biphalin is responsible in part for biphalin's potency. There would have been a reasonable expectation of success given that the tetrapeptide harboring methionine instead of alanine has opioid activity. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 2, 3 and 5-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ronai *et al.* (*Biochem. Biophys. Res. Comm.*, **1979**, *91*, 1239-49), Abbruscato *et al.* (*J. Neurochem.*, **1997**, *69*, 1236-45) and Kanai *et al.* (*J. Biol. Chem.*, **1998**, *273*, 23629-32) as applied to claims 2, 3 and 6-8 above in further view of Hill (U.S. Patent No. 5,880,132), Bock *et al.* (EP 0 434 369 A1) and Ornstein (U.S. Patent No. 5,356,902). Ronai *et al.*, Abbruscato *et al.* and Kanai *et al.* do not teach the administration of (Tyr-D-Met-Gly-Phe-NH-)$_2$ in combination with compounds that block stimulatory amino acid, tachykinin or cholecystokinin receptors (claim 5) or in combination with biphalin. Ornstein teaches stimulatory amino acid antagonists, decahydroisoquinoline compounds, and their use as analgesic compounds (column 2, lines 6 and 7). Hill teaches pharmaceutical compositions comprising both piperidine tachykinin antagonists and opioid analgesics (abstract). Bock *et al.* teach cholecystokinin antagonists and their ability to potentiate morphine and other analgesics. It would have been obvious to one of ordinary skill in the art to combine the (Tyr-D-Met-Gly-Phe-NH-)$_2$ analgesic taught by the combination of Ronai *et al.*, Abbruscato *et al.* and Kanai *et al.* and the stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists taught by Ornstein, Hill and Bock *et al.* or the biphalin taught by Abbruscato *et al.* The skilled artisan would have been motivated to do so given that the prior art teaches that compounds such as (Tyr-D-Met-Gly-Phe-NH-)$_2$ and biphalin

have the same or complimentary functions as stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists. There would have been a reasonable expectation of success given that that stimulatory amino acid, tachykinin or cholecystokinin receptor antagonists and their pharmaceutical use are well-known in the prior art and compatible with opioid analgesics. The MPEP states in section 2144.06: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)" Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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